RESEARCH PAPER

The effects of meloxicam, a non-steroidal anti-inflammatory drug on the biochemical parameters of rabbits

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Abstract

Diclofenac been the predominant cause of vulture population decline in subcontinent has been mostly replaced by several NSAIDs. The present study was aimed to evaluate biochemical effect of meloxicam on functional status of liver and kidney of rabbit. Meloxicam was administered to rabbits divided into two treatment groups. The control group (A) was left untreated. Group B and C were given (1.5mg/kg b.w.) and (3.0mg/kg b.w.) meloxicam respectively for seven consecutive days. Blood samples were collected pre-treatment and on day 1, 3, 5 and 10 post-treatment for the assessment of Serum ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), Bilirubin, ALP (Alkaline Phosphatase), Creatinine and Urea. All the parameters were evaluated from serum samples using Spectrophotometer. Obtained data were subjected to Student Edition of Statistics (SXW). Results showed a significant increase ($P < 0.05$) in ALT, ALP, and Urea on day 1 post treatment with therapeutic dose, whereas with double dose these parameters showed a highly significant ($P < 0.01$) increase on day 1, 3, 5 and significant ($P < 0.05$) increase on day 10. The levels of serum AST, Bilirubin and Creatinine did not show marked elevation with therapeutic meloxicam and were found statistically non-significant ($P > 0.05$). In contrast, double dose caused significant ($P < 0.01$) increase in AST level upto last day. Creatinine showed significant ($P < 0.01$) increase upto day 5 and significant ($P < 0.05$) on day 10. Serum Bilirubin was significantly ($P < 0.01$) increase upto day 3 and significant ($P < 0.05$) only upto day 5 compared with control value. It was concluded that biochemical effects of Meloxicam are dose and time dependent.

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Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a class of drugs having anti-Inflammatory, antipyretic and analgesic properties (Cooper *et al.*, 2009). Diclofenac, an NSAID was reported to be one of the chief cause of vulture population decline in the sub-continent. Therefore, several NSAIDs are now used as substitute, including meloxicam after the ban on diclofenac in 2005-06 in veterinary practice in Pakistan, India and Nepal. Meloxicam is preferential COX-2 inhibitor which is broadly used in cattle, buffalo, goat and dog in a variety of inflammatory conditions. It is an oxicam derivative, which belongs to the enolic acid group of NSAIDs. It is chemically titled as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1, 1dioxide (Mahmood *et al.*, 2010). It is somewhat soluble in acetone, dimethylformamide, and very slightly soluble in ethanol (96%) and methanol. It is insoluble in water at an acid-neutral pH and very highly soluble at a basic pH. Almost all NSAIDs exert their effects via inhibition of the enzyme cyclooxygenase (COX), and this ultimately inhibits the conversion of arachidonic acid (a dietary fatty acid) to prostaglandins during inflammation (Sozer *et al.*, 2011;*Modi et al.*, 2012). Cyclooxygenase exist in two isoforms, COX-1 (constitutive) and COX-2 (induced), however, it is reported that there exist another form called COX-3 which is probably present in the brain and an alternative of the gene for COX-1 but its particular function is still not fully known (Chahade *et al.*, 2008). Meloxicam is relatively selective COX-2 inhibitor at its lowest therapeutic dose and acts as an anti-inflammatory by inhibiting prostaglandin synthesis in inflammatory cells which are directly concerned with inflammation, fever and pain(Mahmood *et al.*, 2010). It has 12 times more selectivity in inhibiting COX-2 activity over COX-1 (Wani *et al.*, 2014).

Meloxicam is frequently indicated for use in ruminants for the treatment of laminitis, mastitis, myositis, pleuritis, pneumonia, premature labor, sprain, synovitis, severe and prolonged inflammation accompanying with musculoskeletal ailments, and for managing post-operative pain.

It has 12 times more selectivity in inhibiting COX-2 activity over COX-1 (Kaymugford *et al.*, 2000; Wani *et al.*, 2014).

Meloxicam though a preferential COX-2 inhibitor and proved safer NSAID as compared to others, still shown extensive nephrotoxic (Ibrahim *et al.*, 2000 and Torres *et al.*, 2013) and hepatotoxic (Hussain *et al.*, 2007; Al-Rekabi *et al.*, 2009)effects in various model animals including rabbits, rats, mice and humans. Meloxicam is also widely used in veterinary practice as management of post-operative pain (Budsberg *et al.*, 2002). Keeping in view the above reports meloxicam might cause deleterious effects on liver and kidney in large animals for longer duration, therefore the present study was designed to evaluate this frequently encountered drug in two different doses using rabbit as a model animal, which will definitely open new ideas regarding extra labelled as well as prescribed usage of NSAIDs.

Materials and methods

The study was conducted in the Department of Veterinary Pharmacology faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tandojam during the year 2016.

Approval of the study

The study plan was approved by Ethical Committee and in the meeting of Board of Study of DAS (Directorate of Advanced Studies), Sindh Agriculture University Tando Jam.

Experimental Animals

Eighteen clinically healthy rabbits of domestic breed with approximately 3-month age, mixed sex and weighing between 2 – 2.5 kg, were purchased from local market of Hyderabad, Sindh Pakistan. The rabbits were kept at Animal House, Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tandojam and were allowed for 15 days to acclimatize. The rabbits were offered carrot, fresh hay, barley and fresh water ad labitum. For baseline/control values of Serum ALT, AST, Bilirubin, ALP, Creatinine and Urea, blood samples were collected from ear vein of the rabbits prior to treatment.

After acclimatization period, the rabbits were divided into three groups i.e. A, B and C having six rabbits in each. Meloxicam an injectable solution was administered intramuscularly to Group B and C @ 1.5mg/kg b.w. (therapeutic dose), and 3.0mg/kg b.w. (double dose of therapeutic dose used in this study) respectively for seven consecutive days with an interval of 24 hours. Whereas Group A was administered with normal saline and served as control group. After 24 hours of last dose administration to treatment groups, blood samples were collected for prescribed times/days 1, 3, 5 and 10th day post treatment.

The blood samples were brought to postgraduate laboratory of Department of Veterinary Pharmacology. Serum was separated by centrifuging the blood at 1500rpm for 10 minutes for biochemical investigation. Serum biochemical parameters were evaluated through respective kit methods Serum ALT (Human: Germany), Serum AST (Human: Germany), Serum Bilirubin (Merck: France), Serum ALP (Human: Germany), Serum Creatinine (Live Diagnostic: Canada), Serum Urea (Human: Germany).

All the samples were run through UV Spectrophotometer (Hitachi Japan).

Statistical analysis
Upon completion, the data was tabulated and statistically analyzed using computer software named Student Edition of Statistics (SXW), Version 8.1 (Copyright 2005, Analytical Software, USA) whereas the levels of significance were set at 0.05 (Significant) and 0.01 (Highly significant).

Results

Serum alanine aminotransferase (ALT)
Administration of 1.5 mg/kg meloxicam to group B produced statistically significant (P<0.05) increase on day 1 in ALT level, however, this increase was reversible and returned gradually to pre-treatment value on subsequent days of sampling. On day 3, 5 and 10 the values were found non-significant. (Fig. 1).Upon administration of double dose 3.0 mg/kg b.w. to group C, a highly significant increase was observed in the level of serum ALT.

The value of ALT was significantly (P<0.01) raised with double dose on day 1, which was persistent till day 3 and 5, on day 10 the mean value was and were found to be statistically significant (P<0.05) as compare to control (Fig. 1).
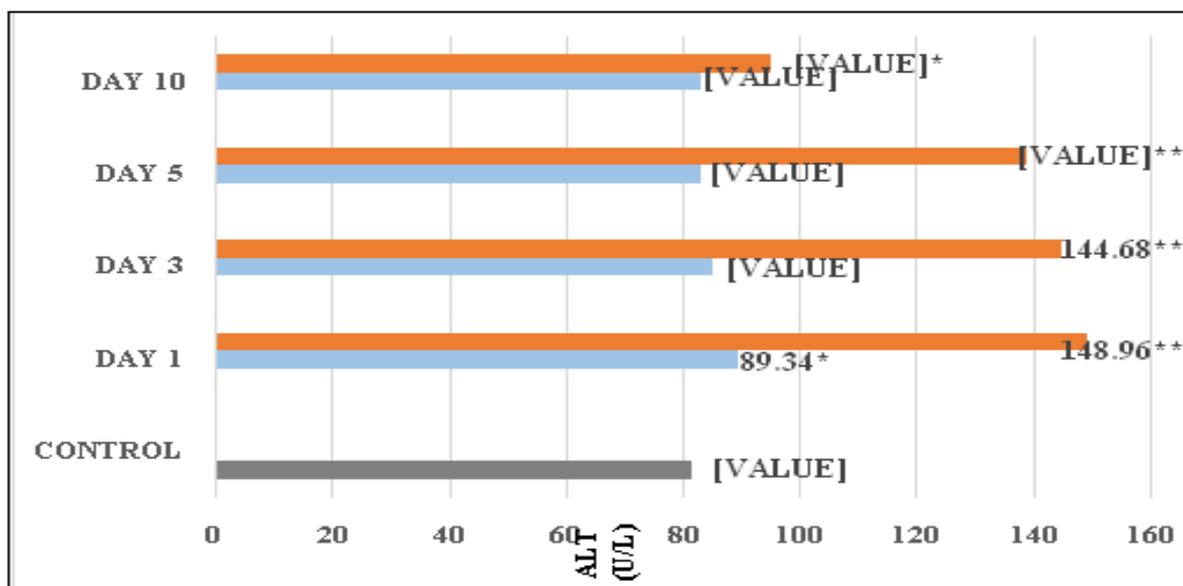
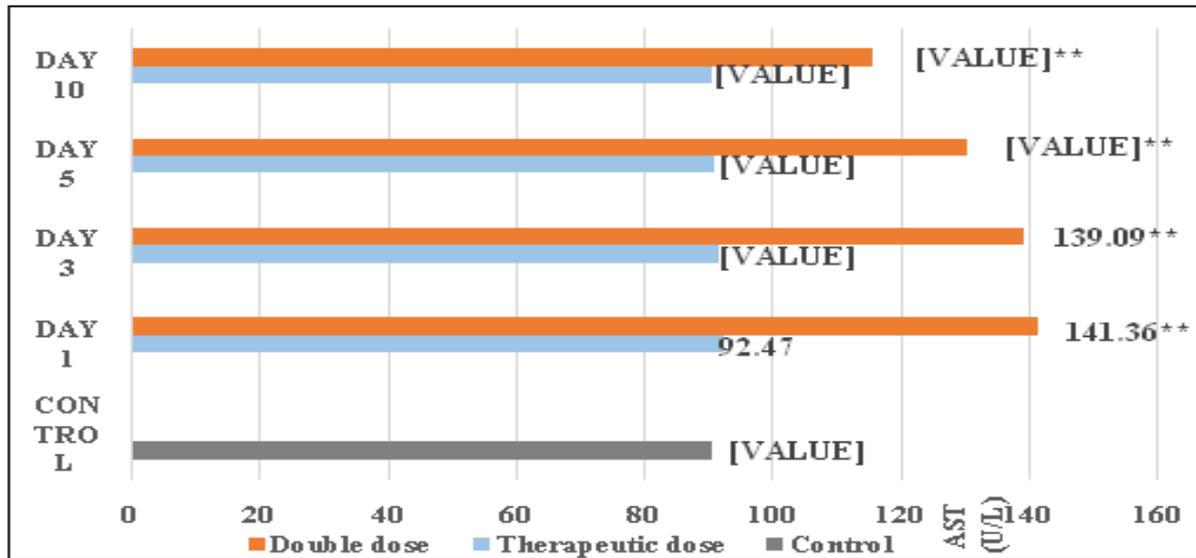*Significantly different from control value (P<0.05)
**Significantly different from control value (P<0.01)
Fig. 1. Mean Serum ALT (U/L) values in rabbits, administered therapeutic and   double dose of meloxicam.

Serum aspartate aminotransferase (AST)

Therapeutic (1.5mg/kg b.w.) administration of I.M injection to group B did not cause prominent alteration of the enzyme, the values were found non-significant on day 1, 3, 5, and 10 post-treatment (Fig. 2).In contrast, double dose (3.0mg/kg b.w.) of meloxicam administered to group C caused shooting up level of AST. The values showed a highly significant ($P<0.01$) increase compared to control value on day 1. The values on day 3 and 5 were found to be significantly ($P<0.01$) increased and even significant ($P<0.01$) on day 10 post treatment (Fig. 2).
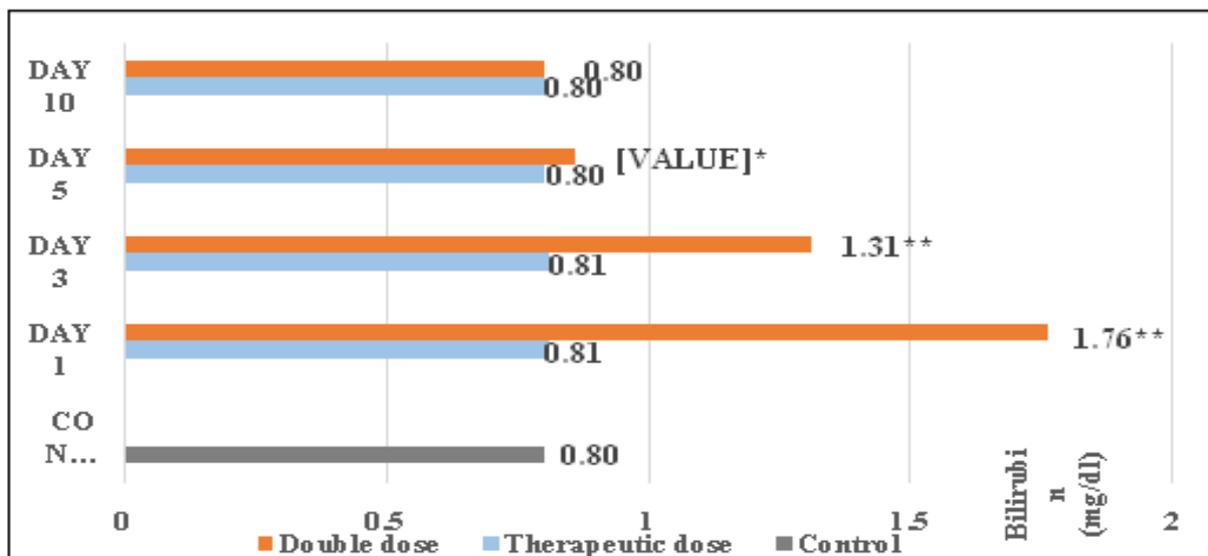

*Significantly different from control value ($P<0.05$)
**Significantly different from control value ($P<0.01$)

Fig. 2. Mean Serum AST (U/L) values in rabbits, administered therapeutic and double dose of meloxicam.

Serum bilirubin

Administration of therapeutic dose (1.5mg/kg I.M) to group B for seven days did not affect serum bilirubin values on day 1. On day 3, 5 and 10 the values were found to be unchanged and were found to be statistically nonsignificant (Fig. 3).

*Significantly different from control value ($P<0.05$)
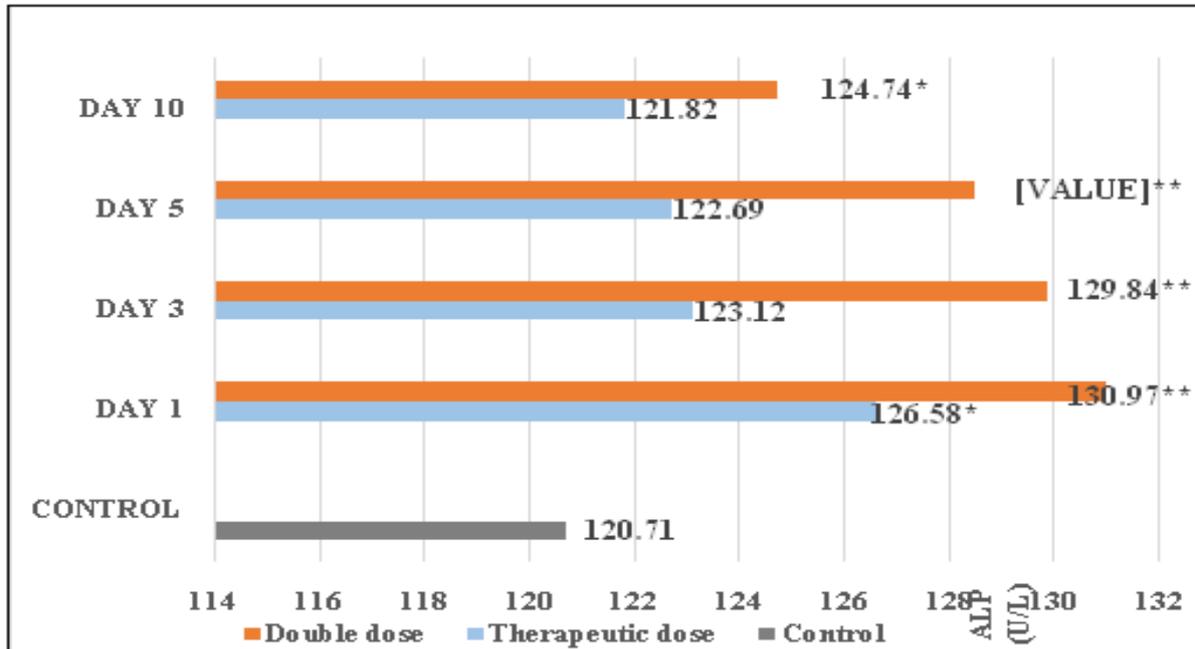**Significantly different from control value ($P<0.01$)

Fig. 3. Mean Serum Bilirubin (mg/dl) values in rabbits, administered therapeutic and double dose of meloxicam.

Group C, receiving double dose of meloxicam for seven days caused a statistically significant (P<0.01) increase in Serum Bilirubin level on day 1 and 3. The values were found to be increased significantly (P<0.05) on day 5 however, on day 10 the levels were dropped almost to control which was again non-significant compared with pre-treatment value (Fig. 3).

Serum alkaline phosphatase (Alp)
The introduction of seven days of therapeutic dose (1.5mg/kg b.w.) meloxicam to group B showed statistically significant (P<0.05) increase in ALP level on day 1.

Whereas on day 3, 5 and 10 the values were found to be statistically non-significant (Fig. 4).

*Significantly different from control value (P<0.05)
**Significantly different from control value (P<0.01)

Fig. 4. Mean Serum Alkaline phosphatase (U/L) values in rabbits, administered therapeutic and double dose of meloxicam.

Intramuscular injection of meloxicam at double dose (3.0mg/kg b.w) once daily for seven consecutive days to group C caused highly significant (P<0.01) difference on day 1 day 3 and day 5) post-medication. The ALP level on day 10 in the double dose treated group was noted to be significantly (P<0.05) increased in comparison with pre-medication/control value (Fig. 4).
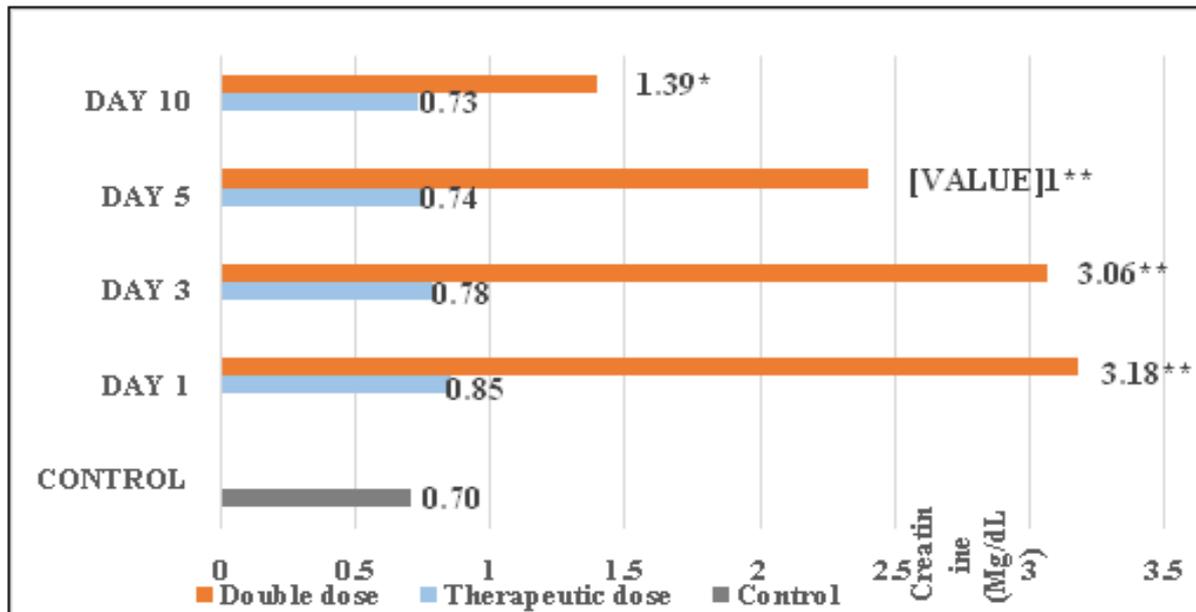
Serum creatinine
Administration of therapeutic dose of 1.5mg/kg meloxicam to group B caused a slight increase in serum creatinine on the 1st day however this increase was reversible and was non-significant. The values of serum creatinine on day 3, 5 and 10 almost returned to pre-treatment values (Fig. 5).

In contrast, administration of double dose (3.0mg/kg) meloxicam to group C for seven days caused marked elevation of Serum Creatinine on day 1 and was significant at (P<0.01) which remained elevated on day 3 and day 5 (2.41±0.06). Again on day 10 the values were found which was statistically significant (P<0.05) compare to control (Fig. 5).

Serum urea
The mean pre-treatment value of Serum Urea was 31.74±0.59 mg/dl. Administration of therapeutic dose 1.5mg/kg b.w meloxicam I/M to group B caused significant (P<0.05) increase in the values of serum urea on day 1 post treatment (35.27±0.4 mg/dl). On subsequent days of sampling i.e day 3, 5 and 10 the values returned to the control value.
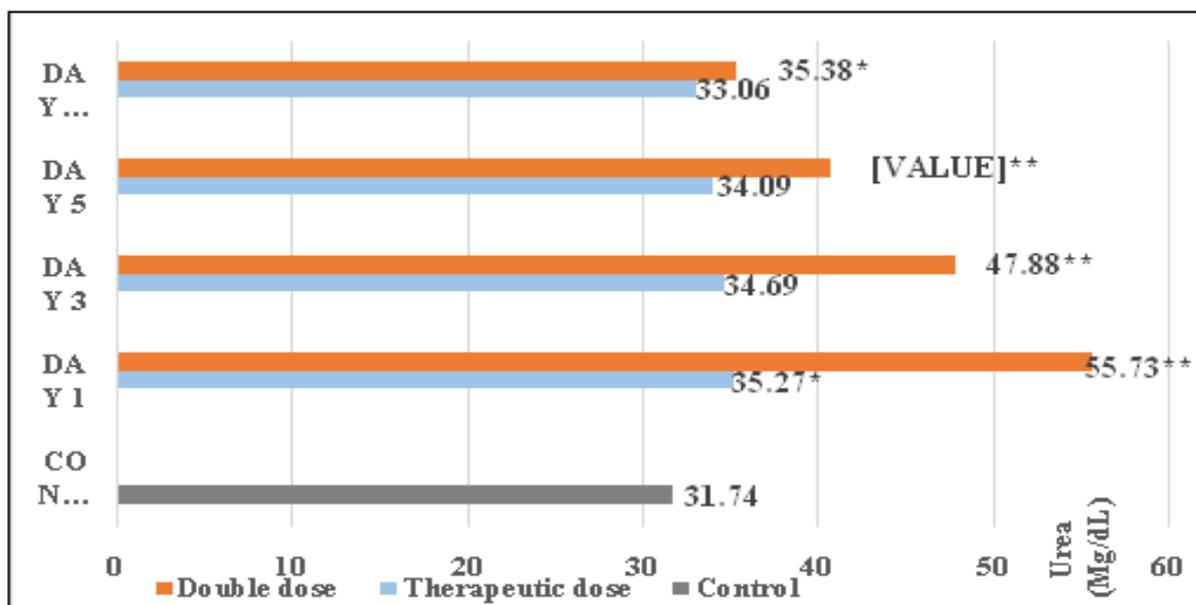
*Significantly different from control value (P<0.05)

**Significantly different from control value (P<0.01)

Fig. 5. Mean Serum Creatinine (Mg/dl) values in rabbits administered therapeutic and double dose of meloxicam.

The difference on these days was found to be statistically non-significant (Fig. 6). On the other hand, administration of double dose 3.0 mg/kg meloxicam for seven days to group C caused a significant (P<0.01) difference in Serum Urea level (55.73±0.86 mg/dl) on day 1 and persistent till day 3 (47.88±1.45 mg/dl), and day 5 (40.79±0.40 mg/dl) post drug administration. The mean value on day 10 was 35.38±0.25mg/dl post drug administration which was continued statistically significant (P<0.05) (Fig. 6).

*Significantly different from control value (P<0.05)

**Significantly different from control value (P<0.01)

Fig. 6. Mean Serum Urea (Mg/dl) values in rabbits, administered therapeutic and double dose of meloxicam**.**

Discussion

Alanine Amino Transferase (ALT)

With therapeutic dose, ALT levels significantly increased (P<0.05) on day 1 however, on day 3, 5 and 10 returned gradually to control. Similar findings were also reported by (Al-Rekabi *et al*., 2009).Almost all NSAIDs are reported to cause elevated levels of aminotransferases that is not clinically relevant and returns to normal upon cessation of therapy. In contrast double dose caused a significant increase (P<0.01) in ALT levels which remain elevated till day 10. This was in agreement with (Ibrahim *et al*., 2000; Al-Rekabi *et al*., 2009; Nora Line, 2013), who found elevated ALT level with meloxicam in rats, rabbits and cats respectively. This persistent increase in ALT level may be attributed to liver toxicity by meloxicam induced liver damage, as ALT elevation is directly related to the cytoplasm of the hepatocytes or due to unstable metabolites of meloxicam which may bind to cell proteins resulting in direct toxicity of liver cells (Odriozola and Lahuerta, 2010).

Aspartate Amino Transferase (AST)

In the case of AST, with therapeutic dose, the values showed non-significant increase and almost returned to pre-treatment value. Meloxicam usage in veterinary practice is remarkably increased in the past few years as it was demonstrated in a variety of animal models to be an eco-friendly substitute for Diclofenac (Mahmood *et al*., 2010). Meloxicam is one of the best substitute to either diclofenac or any other conventional NSAID in animals and avian species. Studies had shown that meloxicam at therapeutic and high doses initiate deleterious effects on vital organs such as liver, kidney and stomach (Burukoglu *et al*., 2014). Numerous studies has been carried out in the past to observe meloxicam in various species. Major alterations for hepatic and renal effects has been indicated by an increased serum ALT, AST, ALP, serum Urea and Creatinine are reported (Ibrahim *et al*., 2000; Turner *et al*., 2006;Al-Rekabi *et al*., 2009; Pehlivan *et al*., 2010; Musa and Ibrahim, 2012; Sinclair *et al*., 2012)in various species. Since meloxicam has a half-life of ±8.0 hours in rabbits and at recommended dose did not accumulates in plasma and almost excrete out.

With double dose significant increase (P<0.01), in AST level was observed which continued till day 10. Compared to the values of ALT the values of AST were lower so that a lower AST to ALT ratio is established. Increased AST levels might be due to oxidative load of drug metabolism in the liver (Hussain *et al*., 2007; Kim *et al*., 2008). NSAIDs-related hepatotoxicity occurs due to metabolic inhibition, oxygen radical toxicity or immunologically mediated damage which results in predominant raise in aminotransferases.

Bilirubin

Bilirubin levels were not affected by therapeutic meloxicam and remained within the limits throughout. This may be due to gradual elimination of meloxicam from blood. With double meloxicam a significant increase (P<0.01) on day 1 and 3 was observed whereas on day 5 the levels dropped however, this was significant (P<0.05). The bilirubin levels decline to pre-treatment value on day 10. The findings of (Ibrahim *et al*., 2000; Abatan *et al*., 2006) are in consistency with our findings. The elevated levels of Bilirubin on initial days might be due to excessive meloxicam which interferes with the cellular antioxidant activity of Bilirubin (Abatan *et al*., 2006).

Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP) increase significantly (P<0.05) only on day 1 and then gradually returned to pre-treatment value Fredholm *et al*., 2013 reported accumulation of 1mg/kg P.O. (Per Oss) meloxicam in plasma up to 5 days and suggested a washout period of 10 days with meloxicam. In the present case on day 10 as the drug is almost completely eliminated from the body the values returned to normal. Effect of meloxicam drops off after drug withdrawal (Musa and Ibrahim, 2012). With double dose significant increase (P<0.01) was observed in group C on 1, 3 and 5 days. The values on day 10 decreased, as compared with initial days however they were significant at (P<0.05). This was supported by Al- Rekabi *et al*., 2009who found significantly increased levels of ALP after inducing a 3 fold higher dose (0.6mg/kg) of meloxicam in rats. Similar observations were also reported by Mahaprabhu *et al*., 2011, who described

significantly increased levels of ALP with therapeutic and double dose of meloxicam in rats. This high upsurge in ALP level might be due to biliary obstruction. Since ALP is secreted in bile duct and meloxicam with high doses may interfere with its biliary secretion.

Creatinine

Therapeutic Meloxicam caused a slight increase in serum creatinine on 1st day, however this increase was non-significant and returned to almost control values. However with double dose of meloxicam significant increase ($P<0.01$) was observed on day 1, 3 and 5 which continued significant ($P<0.05$) till day 10. Creatinine is formed from metabolism of creatine phosphate in muscles and excreted via glomerular filtration at a fairly constant rate. During kidney ailments, creatinine clearance is decreased and most of the creatinine is reabsorbed. Creatinine is considered as gold standard for assessing renalfunctions (Al- Rekabi *et al.*, 2009). Present findings for creatinine were supported by Pehlivan *et al. (*2010) who found significantly elevated levels of creatinine in meloxicam treated rats. This may be due to high concentration of meloxicam which might have interrupted with the glomerular filtration resulting in decrease clearance of creatinine. Though being a preferential COX-2 inhibitor, meloxicam with high doses can also inhibit COX-1 which leads to decreased prostaglandin production especially PGE_2 and PGI_2 (Mahaprabhu *et al.,* 2011 and Sinclair *et al.*, 2012).

Urea

Urea is the end product of protein metabolism which is formed in the liver, absorbed into the blood and carried to kidneys where it is eliminated via glomerular filtration. Meloxicam, when used at therapeutic dose, has weak influence on water and electrolyte balance in kidney and are not indicative of toxicity. Whereas with double dose, prominent rise in urea level might be related to excessive concentrations of meloxicam in the kidney which interfere with the excretion of urea. Nora Line. 2013 stated that meloxicam, when administered with 80% inhibition of COX-2, a 40% inhibition of COX-1, will occur concurrently due to which inhibition of PGE_2 and PGI_2 occur, resulting in renal toxicity.

Conclusion

Based on the results of the present study the following conclusions were drawn:

1. Meloxicam administered at therapeutic dose caused non-significant increase in liver and kidney parameters or if significant in some cases, returned to normal within 3 days post administration.

2. With double dose, the serum liver and kidney markers showed a highly significant altitude in ALT, AST, Bilirubin, ALP, Creatinine and Urea. All the parameters showed a gradual decrease on subsequent days however they were significantly increased even on day 10. Only the values of bilirubin at double dose returned to control value on day 10.

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